EXHIBIT 7

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ORIGINAL ARTICLE

Severe intestinal malabsorption associated with olmesartan: a French nationwide observational cohort study

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ABSTRACT

Objectives Severe sprue-like enteropathy associated with olmesartan has been reported, but there has been no demonstration of an increased risk by epidemiological studies.

Aim To assess, in a nationwide patient cohort, the risk of hospitalisation for intestinal malabsorption associated with olmesartan compared with other angiotensin receptor blockers (ARB) and ACE inhibitors (ACEIs).

Design From the French National Health Insurance claim database, all adult patients initiating ARB or ACEI between 1 January 2007 and 31 December 2012 with no prior hospitalisation for intestinal malabsorption, no serology testing for coeliac disease and no prescription for a gluten-free diet product were included. Incidence of hospitalisation with a discharge diagnosis of intestinal malabsorption was the primary endpoint.

Results 4 546 680 patients (9 010 303 person-years) were included, and 218 events observed. Compared with ACEI, the adjusted rate ratio of hospitalisation with a discharge diagnosis of intestinal malabsorption was 2.49 (95% CI 1.73 to 3.57, p<0.0001) in olmesartan users. This adjusted rate ratio was 0.76 (95% CI 0.39 to 1.49, p=0.43) for treatment duration shorter than 1 year, 3.66 (95% CI 1.84 to 7.29, p<0.001) between 1 and 2 years and 10.65 (95% CI 5.05 to 22.46, p<0.0001) beyond 2 years of exposure. Median length of hospital stay for intestinal malabsorption was longer in the olmesartan group than in the other groups (p=0.02). Compared with ACEI, the adjusted rate ratio of hospitalisation for coeliac disease was 4.39 (95% CI 2.77 to 6.96, p<0.0001) in olmesartan users and increased with treatment duration.

Conclusions Olmesartan is associated with an increased risk of hospitalisation for intestinal malabsorption and coeliac disease.

Significance of this study

What is already known on this subject?
- Cases of olmesartan-induced severe sprue-like enteropathy have been reported.
- The reality of the association has been questioned.
- It is also unknown whether there is an association between enteropathy and other angiotensin receptor blockers (ARBs).

What are the new findings?
- In this large nationwide observational patient cohort, olmesartan exposure is associated with an increased risk of hospitalisation for intestinal malabsorption and coeliac disease.
- This relative risk increases with treatment duration.
- We found no such risk for other ARBs.

How might it impact on clinical practice in the foreseeable future?
- Patients and physicians, including gastroenterologists, should be widely informed of this severe complication.

INTRODUCTION

Olmesartan is an angiotensin II receptor blocker (ARB); its prodrug, olmesartan medoxomil, has been first approved in 2002 in the USA and in 2003 in the European Union, for the treatment of hypertension. Severe sprue-like enteropathies associated with olmesartan have recently been reported.[1 2] The first case series included 22 patients. These patients had severe, chronic diarrhoea and weight loss. Duodenal biopsies showed villous atrophy and inflammation. Coeliac disease serology was negative, and gluten-free diet was ineffective. All patients had taken olmesartan for several months or years. Olmesartan withdrawal was followed by clinical and, when assessed, histological improvement. Nine additional case reports and one literature review have been published[3–8] and confirmed these findings. Olmesartan seems to account for a significant proportion of non-coeliac sprues. In a series of 72 adult patients with villous atrophy and negative coeliac disease serology, olmesartan was prescribed in 16 of these patients, and all but one obtained clinical improvement after olmesartan discontinuation.[9] More recently, a new series of 39 patients with olmesartan-associated sprue has been reported.[10] Interruptions and reintroductions could be studied in a subgroup of 12 patients. Interruptions were followed by remissions, and reintroductions were followed by relapses. These reports suggest that olmesartan may cause severe enteropathy. However, the level of evidence of case reports and small series is limited. The association between olmesartan and enteropathy has also been questioned, as the ROADMAP trial, a

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large randomised controlled trial with several years of follow-up, did not demonstrate any difference in diarrhoea or GI event rates between olmesartan and placebo.[11–13] However, in 2011, the FDA requested a Mini-Sentinel modular programme report of risk assessment because the number of cases of coeliac disease among users of olmesartan was higher than expected in the FDA Adverse Event Report System. The incidence of coeliac disease was found to be similar among all ARBs, including olmesartan.[14 15] Nevertheless, in July 2013, the FDA issued a 'Drug Safety Communication' approving a label change to include sprue-like enteropathy linked to olmesartan.

The association between olmesartan and enteropathy needs to be further investigated. The causality of the association remains uncertain, and its magnitude has not been determined. Moreover, it is unknown whether the association between enteropathy and ARB is limited to olmesartan or also includes other ARBs.

The objective of this study was to assess the risk of enteropathy associated with olmesartan. However, no specific diagnosis code is available for this disease, which was unknown prior to the first published case series. We, therefore, assessed the risk of intestinal malabsorption and coeliac disease associated with the prescription of olmesartan. For this purpose, we compared the rates of hospitalisation with a discharge diagnosis of intestinal malabsorption in patients who were prescribed olmesartan, other ARBs and ACE inhibitor (ACEI) in a large nationwide patient cohort.

METHODS

Data sources

The SNIIRAM (*Système National d'Information Interrégimes de l'Assurance Maladie*) is the French National Health Insurance anonymised claim database. Claims from the general health insurance scheme were used in this study. They include 51.3 million of the 65.7 million inhabitants of France (2013 census), and are available since 2006. Anonymised patient-level records contain billable claims and sociodemographic data such as age and sex. Billable claims include dispensed drugs, laboratory tests (without their results), medical procedures and ambulatory medical care. This database has been previously described.[16 17]

The French hospital discharge database programme médicalisé des systèmes d'information (PMSI) contains information about each patient admitted to a public or private hospital in France, including inpatients and outpatients. This database contains information such as discharge diagnosis (recorded by International Classification of Diseases 10 (ICD-10) code), comorbidities, age, sex, diagnosis-related group, medical procedure performed and length of stay.[16–18]

These two databases were linked in the present study in order to correlate drug prescription with hospitalisation rates and diagnoses. This study was approved by the French data protection agency (*Commission Nationale de l'Informatique et des Libertés*). All databases used in this study only contained anonymous patient records.

Study population

A cohort was constructed from the SNIIRAM, including all adult patients who initiated treatment with an ACEI or ARB between 1 January 2007 and 31 December 2012. The first filled prescription of ACEI or ARB during this period of time constituted the entry date in the cohort (index date). Patients had to be enrolled in the database for at least 1 year before the index date to prevent left censoring. To ensure the absence of left censoring, patients were required to have at least one recorded claim of any type, 1–2 years before the index date. In order to limit the study to incident users of studied drugs, we excluded patients who had filled a prescription containing ACEI or ARB during the 12 months before the index date. Patients with at least one of the following criteria were also excluded: (1) hospitalisation with a discharge diagnosis of intestinal malabsorption (ICD-10 codes K90x) during the year before the index date, (2) any filled prescription containing a gluten-free diet product during the year before the index date, (3) any reimbursed coeliac disease-specific serological testing during the year before the index date.

The ICD codes of coeliac disease and malabsorption were considered as proxies for the diagnosis of olmesartan-associated sprue. It was, therefore, necessary to exclude patients with history of intestinal malabsorption before index date and/or patients with coeliac disease. Therefore, patients who had undergone serological testing or had received gluten-free diet or had been hospitalised with a discharge diagnosis of intestinal malabsorption before the index date were excluded.

Outcomes

The primary outcome was hospitalisation with a discharge diagnosis of intestinal malabsorption (ICD-10 codes K90x). The secondary outcome was hospitalisation with a discharge diagnosis of coeliac disease (ICD-10 code K90.0). Patients were censored at the first event, death or end of the study (31 December 2012 in the main analysis and 31 May 2012 in the sensitivity analysis to avoid information bias).

Exposure assessment

Three kinds of exposures were studied: exposure to olmesartan, exposure to other ARB and exposure to ACEI. Exposure was defined as follows for these three groups. It started from the date of a filled prescription containing a drug of interest (ie, olmesartan, other ARB or ACEI). The end of exposure was defined as the end of prescription duration plus a grace period of 30 days. Grace period is commonly used and recommended in pharmacoepidemiological studies based on claim databases in order to account for incomplete medication adherence and avoid underestimation of drug exposure or misattribution of events. Patient could simultaneously fall into several exposure categories (eg, ACEI+olmesartan). Such periods of overlapping exposure to different drug class were removed from the analysis to prevent misattribution of events. However, they were accounted for in the calculation of treatment duration to prevent classification bias.

Statistical methods

For the primary outcome, a Poisson regression model adjusted for the following potential confounders was used: age, sex, heart failure, dementia, diabetes, immune-mediated diseases (rheumatoid arthritis, Hashimoto thyroiditis, IgA deficiency, dermatitis herpetiformis, lupus, Sjogren, dermatopolymyositis, complement deficiency, angioedema, IBDs), transplantation, ongoing cancer and renal failure. The comorbidities were based on the diagnoses, medical procedures and drug prescriptions from the PMSI and the SNIIRAM.

For the secondary outcome (hospitalisation with a discharge diagnose of coeliac disease), the Poisson regression model was adjusted for age, sex and the following comorbidities: heart failure, diabetes, immune-mediated diseases (rheumatoid arthritis, Hashimoto thyroiditis, IgA deficiency, dermatitis herpetiformis, lupus, Sjogren, dermatopolymyositis, complement deficiency, angioedema, IBDs), active cancer and renal failure.

Dementia and transplantation were removed because of a lack of events. We adjusted for these comorbidities for the following reasons. Patients with immune-mediated abnormalities are at increased risk for coeliac disease. Patients with cancer or allograft recipients are often prescribed drugs that may provoke diarrhoea and malabsorption. Patients with dementia are commonly treated differently from other patients regardless of the disease. Diabetes is a common cause of GI symptoms, including diarrhoea (autonomous neuropathy). Renal failure and heart failure may have influenced the choice of antihypertensive drug.

Poisson regression model fit was assessed by overdispersion analysis, using the deviance/number of degree of freedom ratio and the Pearson χ^2 statistic. Medians were compared by the multisample median test (Brown–Mood test), which assigns 1 for observations greater than the median, and 0 otherwise, and produces χ^2 statistics.[19] Data management and statistical analyses were performed with SAS Enterprise Guide V.4.3.

RESULTS

Study population

A total of 4 552 130 patients initiating ARB or ACEI treatment between 2007 and 2012 were selected from the database; 154 patients who had been hospitalised for intestinal malabsorption during the 12 months preceding inclusion and 4611 patients who had undergone coeliac disease serology testing during the past 12 months were excluded. Finally, 685 patients with a reimbursement claim for a gluten-free diet product in the past 12 months were also excluded. A total of 4 546 680 patients corresponding to 9 129 149 person-years (PY) were included: 118 846 PY of multiple exposures were excluded from the analysis and the remaining 9 010 303 PY of single treatment exposure were distributed as follows: 3 646 311 PY of ACEI exposure, 860 894 PY of olmesartan exposure and 4 503 098 PY of other ARB exposure. The inclusion flow chart is presented in figure 1.

Baseline patient characteristics are presented in table 1. Mean age at inclusion was 63.9 years in the ACEI group, 61.3 years in the olmesartan group and 62.3 years in the other ARB group. The ACEI group comprised fewer women (45.6%) than the olmesartan group (53.9%) and the other ARB group (55.6%). The Poisson regression model was adjusted for both age and sex.

Seventy-seven per cent of the PY in the olmesartan group were included during the 2010–2012 period compared with 72% in the ACEI group and 70% in the other ARB group. Median duration of treatment exposure varied from 326 days (ACEI) to 348 days (olmesartan) and 514 days (other ARBs).

No coding trend of hospital discharge diagnoses of intestinal malabsorption was observed over the study period (see online supplementary table S2).

Incidence of severe malabsorption and coeliac disease

Two hundred eighteen hospitalisations for intestinal malabsorption were observed, 87 in the ACEI group, 48 in the olmesartan group and 83 in the other ARB group, yielding crude incidence rate of 2.4 per 100 000 PY, 5.6 per 100 000 PY and 1.8 per 100 000 PY, respectively.

Olmesartan was associated with an adjusted rate ratio of 2.49 (95% CI 1.73 to 3.57, p<0.0001) of hospitalisation with a discharge diagnosis of intestinal malabsorption compared with ACEI and a rate ratio of 3.17 (95% CI 2.22 to 4.53, p<0.0001) compared with other ARBs. ARBs other than olmesartan were associated with a non-significant rate ratio of 0.78 (95% CI 0.58 to 1.07, p=0.12) of hospitalisation with a discharge diagnosis of intestinal malabsorption, compared with ACEI. Women had a higher rate ratio of hospitalisation with a discharge diagnosis of intestinal malabsorption (rate ratio 1.42, 95% CI 1.08 to 1.87, p=0.01). Inclusion of an interaction term between sex and treatment was added to the model, but was not significant, and was, therefore, not kept in the multivariate model. Gender-stratified results were also calculated. We found no difference between men and women (data not shown). Age had no influence on this rate ratio.

Median length of hospital stay was longer in the olmesartan group (9 days) than in the other ARB group (2 days) and the ACEI group (4 days) (p=0.02).

Hospitalisations with a discharge diagnosis of coeliac disease (ICD-10 code K90.0) were also studied, as olmesartan-associated enteropathy mimics coeliac disease. Adjusted rate ratio of hospitalisation with a discharge diagnosis of coeliac disease was 4.39 (95% CI 2.77 to 6.96, p<0.0001) in patients who were prescribed olmesartan compared with those who were

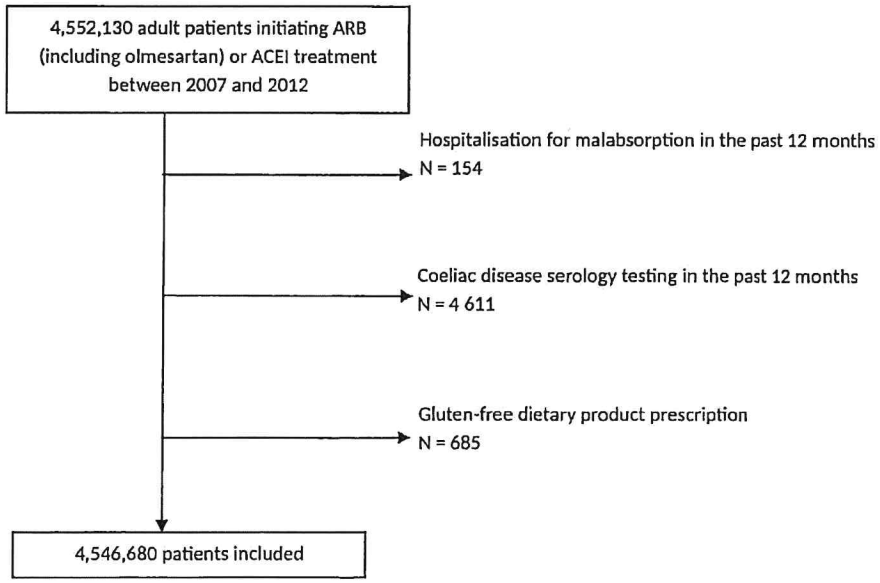

Figure 1 Inclusion flow chart. ACEI, ACE inhibitor; ARB, angiotensin receptor blocker.

Table 1 Population characteristics

	ACEI			Other ARBs			Olmesartan		
	Number of PY	Per cent	Number of events	Number of PY	Per cent	Number of events	Number of PY	Per cent	Number of events
Total	3 646 311	100	87	4 503 098	100	83	860 894	100	48
Women	1 662 055	45.6	40	2 504 538	55.6	59	464 166	53.9	31
Age									
18–39 years	117 367	3.2	8	145 315	3.2	2	30 515	3.5	1
40–49 years	373 726	10.2	8	495 596	11.0	13	108 604	12.6	6
50–59 years	822 079	22.5	22	1 082 446	24.0	13	227 431	26.4	7
60–69 years	921 633	25.3	25	1 195 828	26.6	19	235 147	27.3	12
70–79 years	788 347	21.6	14	975 638	21.7	24	172 525	20.0	14
≥80 years	623 159	17.1	10	608 274	13.5	12	86 672	10.1	8
Inclusion year									
2007	123 472	3.4	3	165 809	3.7	4	22 987	2.7	1
2008	337 993	9.3	17	461 097	10.2	9	66 881	7.8	1
2009	544 289	14.9	12	706 453	15.7	18	111 884	13.0	3
2010	729 240	20.0	23	906 922	20.1	21	161 780	18.8	10
2011	878 875	24.1	13	1 067 364	23.7	13	216 958	25.2	18
2012	1 032 443	28.3	19	1 195 453	26.5	18	280 405	32.6	15

ACEI, ACE inhibitor; ARB, angiotensin receptor blocker; PY, person-years.

prescribed ACEI and 4.82 (95% CI 3.12 to 7.45, p<0.0001) compared with other ARBs. This ratio was 0.91 (95% CI 0.58 to 1.42, p=0.68) in patients who were prescribed other ARBs compared with those who were prescribed ACEI. See table 4 for details.

The first case report linking olmesartan and enteropathy was published online on 25 June 2012. We, therefore, performed a sensitivity analysis in which the study period and follow-up ended on 31 May 2012, which gave very similar results (see online supplementary tables S3–S5).

Risk over time

Descriptive data were in favour of non-homogeneity of risk according to the duration of treatment exposure (table 2). To account for such changes in risk and to assess the kinetics of the risk of hospitalisation with a discharge diagnosis of intestinal malabsorption associated with olmesartan exposure, the model was stratified on treatment exposure. The following duration strata were used: less than 1 year, between 1 and 2 years, and 2 years or more. Compared with ACEI, the adjusted rate ratio of hospitalisation with a discharge diagnosis of intestinal malabsorption associated with olmesartan exposure was 0.76 (95% CI 0.39 to 1.49, p=0.43) for treatment duration shorter than 1 year, 3.66 (95% CI 1.84 to 7.29, p<0.001) between 1 and 2 years of treatment exposure and 10.65 (95% CI 5.05 to 22.46, p<0.0001) beyond 2 years of treatment exposure (table 3). Very similar results were obtained when follow-up ended on 31 May 2012 (see online supplementary tables S4 and S5). Compared with ACEI, the rate ratio of hospitalisation with a discharge diagnosis of coeliac disease was 1.98 (95% CI 0.85 to 4.61, p=0.11) for treatment shorter than 1 year; 4.36 (95% CI 2.04 to 9.34, p<0.001) for treatment between 1 and 2 years and 10.21 (95% CI 4.21 to 24.76, p<0.0001) for more than 2 years of olmesartan exposure (table 4). Details of discharge diagnoses by duration of treatment exposure in each group are presented in online supplementary table S1. No overdispersion was observed in any Poisson regression models.

Table 2 Risk over time: descriptive data

	ACEI	Olmesartan	ARB
PY	3 646 311	860 894	4 503 098
0–1 year	1 584 921	377 748	1 706 722
1–2 years	922 124	223 477	1 153 054
≥2 years	1 139 266	259 668	1 643 322
Number of events	87	48	83
0–1 year	59	10	36
1–2 years	18	15	23
≥2 years	10	23	24
Crude incidence rate (per 100 000 PY)	2.39	5.58	1.84
0–1 year	3.72	2.65	2.11
1–2 years	1.95	6.71	1.99
≥2 years	0.88	8.86	1.46

ACEI, ACE inhibitor; ARB, angiotensin receptor blocker; PY, person-years.

DISCUSSION

In this large nationwide cohort of patients, olmesartan users were found to have an increased risk of hospitalisation for intestinal malabsorption and coeliac disease compared with ACEI. These risks increased with duration of olmesartan exposure up to 10-fold beyond 2 years of exposure. Users of ARBs other than olmesartan did not exhibit an increased risk of hospitalisation for intestinal malabsorption or coeliac disease. These results were adjusted for potential confounders. During the first year of treatment, patients treated with other ARBs had a decreased rate of hospitalisation for intestinal malabsorption compared with patients treated with ACEI. There was an excess of diagnoses of malabsorption other than coeliac disease among ACEI users (ICD-10 codes K90.4, K90.8 and K90.9; see online supplementary table S1). However, no significant difference in terms of risk of hospitalisation for coeliac disease (ICD-10 code K90.0) was observed between users of ARBs other than olmesartan and ACEI users. The reason for this is unclear, but it does not affect the consistency of the results. It may have

Table 3 Crude and adjusted rate ratios of hospitalisation with a discharge diagnosis of intestinal malabsorption over time (ref: ACEI)

	Crude rate ratio	95% CI	p Value	Adjusted rate ratio	95% CI	p Value
Overall population						
Olmesartan	2.34	(1.64 to 3.32)	<0.0001	2.49	(1.73 to 3.57)	<0.0001
Other ARBs	0.77	(0.57 to 1.04)	0.09	0.78	(0.58 to 1.07)	0.12
Treatment duration <1 year						
Olmesartan	0.71	(0.36 to 1.39)	0.32	0.76	(0.39 to 1.49)	0.43
Other ARBs	0.57	(0.37 to 0.86)	0.007	0.58	(0.38 to 0.88)	0.01
Treatment duration 1–2 years						
Olmesartan	3.44	(1.73 to 6.82)	0.0004	3.66	(1.84 to 7.29)	<0.001
Other ARBs	1.02	(0.55 to 1.89)	0.95	1.03	(0.56 to 1.92)	0.92
Treatment duration >2 years						
Olmesartan	10.09	(4.80 to 21.20)	<0.0001	10.65	(5.05 to 22.46)	<0.0001
Other ARBs	1.66	(0.80 to 3.48)	0.18	1.68	(0.80 to 3.51)	0.18

ACEI, ACE inhibitor; ARB, angiotensin receptor blocker.

underestimated the rate ratio associated with olmesartan as compared with ACEI.

The strength of the association and the consistency with reported cases (including the long lag time between initiation of olmesartan and diagnosis of malabsorption) are strong arguments in favour of causality. In addition, the longer length of hospital stay in patients who were prescribed olmesartan suggests that their disease was distinct from and more severe than that observed in patients receiving ARBs or ACEI. Patients who obtained clinical improvement after stopping olmesartan and who experienced subsequent recurrence of symptoms on olmesartan rechallenge have also been described.[6 7] In the aforementioned ROADMAP trial, no significant difference in the rate of GI adverse events or diarrhoea was observed between olmesartan and placebo.[10–12] However, these adverse events are common in patients with diabetes (reported in 3.5% and 2.3% of patients in the olmesartan arm of this trial, respectively), and may have confounded the effect of olmesartan on the risk of severe enteropathy. This more specific risk was not assessed in this trial, which did not have sufficient statistical power to detect such an association. For the same reasons, a recent cohort study did not find any significant difference in the risk of GI disease-related hospitalisation among patients with diabetes treated by olmesartan compared with patients with diabetes treated by other ARBs.[20]

Table 4 Adjusted rate ratios of hospitalisation with a discharge diagnosis of coeliac disease (ref: ACEI)

	Adjusted rate ratio	95% CI	p Value
Overall population			
Olmesartan	4.39	(2.77 to 6.96)	<0.0001
Other ARBs	0.91	(0.58 to 1.42)	0.68
Treatment duration <1 year			
Olmesartan	1.98	(0.85 to 4.61)	0.11
Other ARBs	1.07	(0.56 to 2.05)	0.84
Treatment duration 1–2 years			
Olmesartan	4.36	(2.04 to 9.34)	<0.001
Other ARBs	0.77	(0.36 to 1.67)	0.51
Treatment duration >2 years			
Olmesartan	10.21	(4.21 to 24.76)	<0.0001
Other ARBs	0.94	(0.36 to 2.47)	0.90

ACEI, ACE inhibitor; ARB, angiotensin receptor blocker.

This study has several strengths. First, it was based on a large nationwide database. Second, we adjusted for potential confounders that may affect the outcome (hospitalisation with a discharge diagnosis of malabsorption) or the prescription of antihypertensive drugs. Finally, to prevent selection bias, we excluded those patients with malabsorption and those at risk for coeliac disease before the index date.

Several potential limitations of this study should also be discussed. First, this study was based on administrative data, which may result in information bias. There is no direct comparison between these data and chart review in France for the diagnosis of intestinal malabsorption or coeliac disease. However, the possible lack of sensitivity is unlikely to affect the three groups of the study differently; as such, it does not result in bias in the analysis, and could not refute the message of the study. Another issue raised by healthcare electronic records concerns trends in coding practice. However, in this study, no coding trend was observed for intestinal malabsorption among adult patients in France during the study period (see online supplementary table S2). Second, the potential indication bias should be discussed. However, ACEI and ARB share very similar therapeutic indications. Coeliac disease is more frequent in women and in younger subjects,[21] but analyses were adjusted for age and sex. In addition, there is no reason why coeliac disease-predisposing HLA genotype would be overrepresented in patients who were prescribed olmesartan. Finally, it is unlikely that all cases of olmesartan-associated enteropathy were captured by hospital diagnoses of intestinal malabsorption and coeliac disease. It is likely that milder forms also exist. Overall number needed to harm was 31 350 patient-years of olmesartan exposure. Beyond 2 years of exposure, this number was 12 500 patient-years. However, caution is needed to interpret these values as this study was not aimed to measure the incidence of olmesartan-associated enteropathy, but rather to estimate the strength of the association between olmesartan and severe forms of enteropathy and malabsorption. As a consequence, this study underestimates the true incidence and only provides the incidence of the most severe forms of olmesartan-associated enteropathy.

In summary, this paper shows, with a higher level of evidence, the association between severe intestinal malabsorption and olmesartan exposure. These results have important practical consequences as olmesartan is widely prescribed worldwide. In France, olmesartan was prescribed to more than 800 000 patients in 2012. Patients treated with olmesartan should be informed about the risk of this complication, and should be

advised to seek medical attention if they experience GI symptoms. This information should also be widely delivered to physicians of all disciplines, particularly to gastroenterologists who are faced to this new category of patients.

However, further studies are required to assess the frequency and clinical spectrum of milder forms. The pathophysiology of olmesartan-associated enteropathy also requires further investigation: the clinical and pathological features are remarkably similar to those of coeliac disease or refractory sprue, but the underlying cause and mechanisms are different. We expect such studies to shed new light on coeliac disease.

Contributors FC and HA had the idea for the study. MB conceived and planned the study and drafted the manuscript. MM performed data management and statistical analyses. All authors contributed to interpretation of the data and revised the manuscript. All authors approved the final manuscript.

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Competing interests None declared.

Ethics approval This research was authorised by the French Data Protection Agency (CNIL).

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Data sharing statement FC had full access to all of the data in the study, and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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GUT

Severe intestinal malabsorption associated with olmesartan: a French nationwide observational cohort study

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EXHIBIT 8

U.S. Food and Drug Administration
Protecting and Promoting Your Health

Drug Safety Communications

FDA Drug Safety Communication: FDA approves label changes to include intestinal problems (sprue-like enteropathy) linked to blood pressure medicine olmesartan medoxomil

Safety Announcement

[7-3-2013] The U.S. Food and Drug Administration (FDA) is warning that the blood pressure drug olmesartan medoxomil (marketed as Benicar, Benicar HCT, Azor, Tribenzor, and generics) can cause intestinal problems known as sprue-like enteropathy. FDA has approved changes to the labels of these drugs to include this concern.

Symptoms of sprue-like enteropathy include severe, chronic diarrhea with substantial weight loss. The enteropathy may develop months to years after starting olmesartan, and sometimes requires hospitalization (see Data Summary). If patients taking olmesartan develop these symptoms and no other cause is found, the drug should be discontinued, and therapy with another antihypertensive started. Discontinuation of olmesartan has resulted in clinical improvement of sprue-like enteropathy symptoms in all patients.

Olmesartan medoxomil is an angiotensin II receptor blocker (ARB) approved for the treatment of high blood pressure, alone or with other antihypertensive agents, and is one of eight marketed ARB drugs. Sprue-like enteropathy has not been detected with ARB drugs other than olmesartan.

FDA will continue to evaluate the safety of olmesartan-containing products and will communicate again if additional information becomes available.

FACTS about Olmesartan

- Olmesartan is an angiotensin II receptor blocker (ARB) approved for the treatment of hypertension, alone or with other antihypertensive agents, to lower blood pressure. Lowering blood pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and heart attacks.
- In 2012, a total of approximately 10.6 million prescriptions were dispensed, and approximately 1.9 million patients received a dispensed prescription for olmesartan-containing products from U.S. outpatient retail pharmacies.[1] According to sales data, the majority of olmesartan-containing products were distributed to outpatient retail pharmacies (81.5% retail, 15% mail order/specialty pharmacies and 3.5% non-retail) during this time.[2]

Additional Information for Patients

- Contact your health care professional right away if you take an olmesartan-containing product and experience severe diarrhea, diarrhea that does not go away, or significant weight loss.
- Your health care professional may evaluate your symptoms to determine the cause. If no other cause is found, you may be asked to stop taking olmesartan and start taking a different high blood pressure medicine.
- Do not stop taking your high blood pressure medicine without first discussing it with your health care professional. When high blood pressure is not appropriately treated, strokes, heart attacks or kidney failure, or other serious harm can result.
- Discuss any questions or concerns about olmesartan with your health care professional.
- Report any side effects you experience to your health care professional and the FDA MedWatch program, using the information in the "Contact FDA" box at the bottom of the page.

Additional Information for Health Care Professionals

- Tell your patients to contact you if they develop severe, chronic diarrhea with substantial weight loss while taking an olmesartan-containing product, even if it takes months to years for symptoms to develop.
- If a patient develops these symptoms during treatment with olmesartan, other etiologies, such as celiac disease, should be investigated. If no other etiology is identified, olmesartan should be discontinued and another antihypertensive treatment started.
- Symptoms of sprue-like enteropathy may develop months to years after starting olmesartan.
- Report adverse events involving olmesartan-containing products to the FDA MedWatch program, using the information in the "Contact FDA" box at the bottom of the page.

Data Summary

Olmesartan medoxomil is an angiotensin II receptor blocker (ARB) that was approved on April 25, 2002, for the treatment of hypertension, alone or with other antihypertensive agents. The current olmesartan drug labels include diarrhea in the Adverse Reactions section.

FDA evaluated adverse event reports received by FDA's Adverse Event Reporting System (FAERS), published literature case series,[3-4] information from FDA's Mini-Sentinel pilot of the Sentinel Initiative, and information from the CMS Medicare database. FDA's evaluation found clear evidence of an association between olmesartan and sprue-like enteropathy.

FDA identified 23 serious cases in FAERS presenting as late-onset diarrhea with significant weight loss and, in some cases, with intestinal villous atrophy on biopsy. All patients improved clinically after discontinuation of olmesartan, and a positive rechallenge was seen in 10 of the cases.

In June 2012, Mayo Clinic researchers published a case series of sprue-like enteropathy associated with olmesartan in 22 patients whose clinical presentation was similar to that of the FAERS cases: Patients in the Mayo Clinic case series developed diarrhea, weight loss, and villous atrophy while on olmesartan, and drug discontinuation resulted in clinical improvement.[3] Eighteen patients had follow-up intestinal biopsies histologically demonstrating recovery or improvement of the duodenum after discontinuation of olmesartan.

In May 2013, an article describing patients with villous atrophy and negative serologies for celiac disease reported that some patients without definitive etiologies for villous atrophy were characterized as having unclassified sprue. Some of these patients were later found to have villous atrophy associated with olmesartan use.[4]

The signal of sprue-like enteropathy with olmesartan was further investigated for a possible ARB class effect using active surveillance data. Mini-Sentinel and CMS Medicare data were assessed for celiac disease (as a marker for enteropathy and other gastrointestinal symptoms) after exposure to ARBs. Mini-Sentinel and CMS Medicare assessments of ICD-9 codes for celiac disease showed that at a 2-year minimum exposure, which correlates with the long latency observed in literature and case reports, olmesartan users had a higher rate of celiac disease diagnoses in claims and administrative data than users of other ARBs. Interpretation is limited by the small number of events observed at longer exposure periods and the uncertainty about the validity of codes for celiac disease, but these results support other data in suggesting a lack of a class effect.

Although the mechanism for olmesartan-associated sprue-like enteropathy is uncertain, the long latency before onset of symptoms, findings of lymphocytic or collagenous colitis, and high association with HLA-DQ2/8 suggest a localized delayed hypersensitivity or cell-mediated immune response to the pro-drug olmesartan medoxomil. Rubio-Tapia et al., suggest that ARB-mediated inhibition of TGF-β, an important mediator of gut homeostasis, is a possible mechanism for olmesartan-associated sprue-like enteropathy, although it is unclear why this effect is not observed with other ARBs.[3]

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EXHIBIT 9

ORIGINAL ARTICLE

MAYO CLINIC

Severe Spruelike Enteropathy Associated With Olmesartan

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Abstract

Objective: To report the response to discontinuation of olmesartan, an angiotensin II receptor antagonist commonly prescribed for treatment of hypertension, in patients with unexplained severe spruelike enteropathy.

Patients and Methods: All 22 patients included in this report were seen at Mayo Clinic in Rochester, Minnesota, between August 1, 2008, and August 1, 2011, for evaluation of unexplained chronic diarrhea and enteropathy while taking olmesartan. Celiac disease was ruled out in all cases. To be included in the study, the patients also had to have clinical improvement after suspension of olmesartan.

Results: The 22 patients (13 women) had a median age of 69.5 years (range, 47-81 years). Most patients were taking 40 mg/d of olmesartan (range, 10-40 mg/d). The clinical presentation was of chronic diarrhea and weight loss (median, 18 kg; range, 2.5-57 kg), which required hospitalization in 14 patients (64%). Intestinal biopsies showed both villous atrophy and variable degrees of mucosal inflammation in 15 patients, and marked subepithelial collagen deposition (collagenous sprue) in 7. Tissue transglutaminase antibodies were not detected. A gluten-free diet was not helpful. Collagenous or lymphocytic gastritis was documented in 7 patients, and microscopic colitis was documented in 5 patients. Clinical response, with a mean weight gain of 12.2 kg, was demonstrated in all cases. Histologic recovery or improvement of the duodenum after discontinuation of olmesartan was confirmed in all 18 patients who underwent follow-up biopsies.

Conclusion: Olmesartan may be associated with a severe form of spruelike enteropathy. Clinical response and histologic recovery are expected after suspension of the drug.

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Olmesartan is one of several angiotensin II receptor antagonists used for management of hypertension since 2002.[1] Diarrhea is a common adverse effect of many medications, although the mechanisms underlying diarrhea remain unclear in most cases. Enteropathy as a cause of drug-induced diarrhea has been reported previously with the use of azathioprine and mycophenolate mofetil.[2-4] We first suspected the possible connection between enteropathy and olmesartan when 2 consecutive patients referred to our institution for evaluation of presumed refractory celiac disease reported unexplained clinical improvement during hospitalization but prompt relapse following hospital discharge. They asked if the disease course could have been due to their hypertensive medications, which were withheld on hospitalization because of hypotension. At the same time, we were studying a cohort of patients with collagenous sprue and discovered olmesartan use in one-third of the patients with a recent diagnosis of the disorder.[5] As additional patients were identified with similar clinical features (eg, chronic diarrhea, weight loss, unexplained spruelike enteropathy with or without abnormal subepithelial collagen deposition, negative celiac serology, and lack of response to gluten exclusion), a perceived association between these features and olmesartan evolved. It also became clear that these patients were unlikely to have celiac disease, as all lacked IgA tissue transglutaminase antibodies and had never responded to a gluten-free diet. The clinical observation of improvement of gastrointestinal symptoms and subsequent demonstration of histologic recovery after olmesartan withdrawal prompted us to advise our patients with unexplained spruelike enteropathy to discontinue olmesartan. We reported our observation to US Food and Drug Administration officials and submitted reports using the MedWatch system.

In this article, we describe the clinical manifestations in 22 patients with unexplained spruelike enteropathy that improved clinically after discontinuation of olmesartan.

PATIENTS AND METHODS

This study was approved by the Mayo Clinic Institutional Review Board. Patients were considered for inclusion in the study if they had chronic diarrhea (>4 weeks) while taking olmesartan and met 2 additional criteria. First, the cause of their enteropathy

could not be established after a systematic diagnostic evaluation that included investigation for disorders associated with nonresponsive celiac disease as previously reported by our group.[6] Second, they had to improve clinically after discontinuation of olmesartan. Most of these patients had undergone extensive evaluation by their referring physicians and had had several therapeutic trials, without benefit. The electronic medical records of 24 such patients seen at Mayo Clinic in Rochester, Minnesota, between August 1, 2008, and August 1, 2011, were reviewed by one physician (M.L.H.). Two of the 24 patients were excluded from the study, 1 who had tropical sprue and 1 who improved clinically and histologically with oral budesonide before suspension of olmesartan.

Data Abstraction

Clinical and laboratory data were abstracted from the medical record. Only data that reflected conditions that existed before suspension of olmesartan were included as baseline data. We defined categories of body weight using body mass index and World Health Organization criteria.[7] Anemia was defined in women as a hemoglobin level of less than 12 g/dL (to convert to g/L, multiply by 10) and in men as a hemoglobin level of less than 13.5 g/dL. Hypoalbuminemia was defined as an albumin value lower than 3.5 g/dL (to convert to g/L, multiply by 10). HLA-DQ typing,[8] celiac disease serology (tissue transglutaminase antibodies or deamidated gliadin peptide antibodies by enzyme-linked immunosorbent assay and endomysial antibodies on monkey esophagus by indirect immunofluorescence),[9-11] and assessment of response to a gluten-free diet were investigated. Anti-enterocyte antibodies were tested using primate intestine by indirect immunofluorescence and were performed at The Children's Hospital of Philadelphia, as reported by Akram et al.[12] *Severe enteropathy* was defined by the presence of at least one of the following criteria: (1) need for hospitalization because of severe dehydration, electrolyte imbalance, and/or acute renal failure, (2) need for total parenteral nutrition, and (3) weight loss of more than 10 kg.

Histopathology

Pathology material (biopsy samples from the gastrointestinal tract) was reviewed by one of the authors (T.-T.W.). The number of intraepithelial lymphocytes per 100 epithelial cells, degree of villous atrophy graded with the modified Marsh classification,[13] presence of subepithelial collagen, degree of lamina propria inflammation, and presence of acute inflammation were assessed. The presence of aberrant or clonal intraepithelial lymphocytes was investigated by CD3 and CD8 immunostaining[14] and polymerase chain reaction,[15] respectively. When multiple small bowel biopsies were performed as part of the diagnostic evaluation and before withdrawal of the drug, the baseline biopsy was considered to be the small bowel biopsy performed closest to the date of suspension of olmesartan. Follow-up biopsies were defined as biopsies performed at least 30 days after the date of suspension of olmesartan. Other disorders of the gastrointestinal tract (when present) were diagnosed using accepted pathologic criteria (eg, microscopic colitis).[16]

Outcomes After Suspension of Olmesartan

Clinical response was defined as the resolution of diarrhea. Weight gain was considered a positive finding. *Remission* required both a clinical response and confirmation by normal findings on intestinal biopsy during follow-up. All patients who had been on a gluten-free diet were followed up after reintroduction of gluten and withdrawal of corticosteroids.

Medication Use

We reviewed the medication history of all patients, including the duration of treatment, dosage, and response of diarrhea to a trial of olmesartan withdrawal. Alternative antihypertensive drugs used after suspension of olmesartan are reported.

Statistical Analyses

Data were summarized using descriptive statistics, including total numbers and percentages for categorical variables and median or mean (range) for continuous variables.

RESULTS

The 22 patients (13 women) had a median age of 69.5 years (range, 47-81 years). Twenty-one of the patients were non-Hispanic white, and 1 patient was black. Patients were residents of 16 different US states (Table 1).

The most frequent clinical diagnoses at time of referral were nonresponsive/refractory celiac disease (n=10) and unexplained sprue (n=6). Most patients were taking 40 mg/d of olmesartan (range, 10-40 mg/d) for several months or years before the onset of diarrhea. Detailed information about the duration of exposure to olmesartan before onset of diarrhea was available in the medical record in 14 patients (64%). Among these, the mean duration was 3.1 years (range, 0.5-7 years). An additional 5 patients were taking olmesartan for at least 1 year before the onset of symptoms. Information about duration of exposure to olmesartan before onset of diarrhea was not available in 3 patients.

TABLE 1. Demographic Characteristics, Outcome, and Alternative Antihypertensive Drugs Used After Suspension of Olmesartan in 22 Patients With Spruelike Enteropathy

Patient No./ sex/age (y)	Weight loss (kg)	Outcome after suspension of olmesartan[a]	Alternative antihypertensive drug
1/F/59	14	Remission	Metoprolol
2/F/62	11	Clinical response	None
3/F/72	31	Remission, weight gain (13.3 kg)	Bisoprostol-hydrochlorothiazide
4/M/66[b]	18	Remission, weight gain (11 kg)	Metoprolol
5/M/81	2.5	Remission, weight loss (4.1 kg)	Lisinopril, metoprolol
6/M/64	14	Clinical response	Amlodipine
7/F/65	11	Remission, weight gain (4.2 kg)	Amlodipine, hydrochlorothiazide
8/M/76	12	Remission, weight gain (13.4 kg)	Amlodipine, hydrochlorothiazide
9/M/64	20.5	Remission, weight gain (15.7 kg)	Amlodipine, hydrochlorothiazide
10/F/72	30	Remission, weight gain (28 kg)	Amlodipine, atenolol, hydrochlorothiazide
11/M/74	15	Clinical response	Hydrochlorothiazide
12/M/58	57	Remission, weight gain (23.4 kg)	Amlodipine, metoprolol
13/F/77	29	Remission, weight gain (9.7 kg)	Atenolol, hydrochlorothiazide
14/F/76	7	Remission, weight gain (2.9 kg)	Hydrochlorothiazide
15/M/68	18	Remission, weight gain (14.9 kg)	Metoprolol
16/F/71	9	Remission, weight gain (11.9 kg)	Triamterene, hydrochlorothiazide
17/F/66[b]	20.5	Clinical response, weight gain (13.4 kg)	Spironolactone, carvedilol
18/F/64[c]	50	Clinical response, weight gain (4 kg)	Amlodipine
19/F/75	41	Remission	None
20/M/47	32	Remission, weight gain (13.9 kg)	Metoprolol, amlodipine, doxazosin
21/F/71	18	Remission, weight gain (10.2 kg)	Atenolol, hydralazine
22/F/74	40	Remission, weight gain (6.3 kg)	None

[a] Weight change (defined by weight at diagnosis minus weight at last follow-up visit) is provided when available in the medical record.
[b] Case previously published.[5]
[c] Non-Hispanic black.

Clinical Manifestations

Diarrhea had been present for a median of 19.2 months (range, 3-53 months) before suspension of the drug. At the time of presentation, all patients had diarrhea and weight loss (median weight loss, 18 kg; range, 2.5-57 kg). Nausea and vomiting were present in 15 patients (68%), abdominal pain in 11 (50%), bloating in 9 (41%), and fatigue in 15 (68%). The onset of diarrhea was sudden in 9 patients. The stool frequency was extremely abnormal, with a median of 6 evacuations per day (range, 3-42 evacuations per day). Among 8 patients with timed stool collection, the mean stool weight was 933.1 g/24 h (range, 225-3225 g/24 h), and mean fecal fat was 28.3 g/24 h (range, 8-50 g/24 h). Although timed stool weight was not investigated in all patients, 14 patients (64%) required hospitalization because of severe dehydration (4 patients had acute renal failure). Total parenteral nutrition was necessary in 4 patients. At the time of the first visit at Mayo Clinic, 11 of the patients had normal weight, 6 were underweight, 4 were overweight, and 1 was obese. All but one patient (patient 16) met criteria for severe enteropathy.

Laboratory Findings

Results of IgA tissue transglutaminase antibody testing were negative in all patients. IgA endomysial antibody results were negative in all 9 patients who underwent testing. HLA-DQ typing was performed in 21 patients: DQ2 was present in 15 patients, DQ8 in 2 patients, and neither DQ2 nor DQ8 in 4 patients. Anti-enterocyte antibody testing was done in 19 patients (86%), and results were negative in 16 (including 7 patients who had a positive nonspecific nuclear pattern of unknown clinical significance) and positive with a linear/apical pattern in 3.

Fourteen patients (64%) had normocytic normochromic anemia (2 had elevated red blood cell distribution width suggesting anisocytosis); the lowest hemoglobin level was 9.3 g/dL. Ten patients (45%) had hypoalbuminemia; the lowest albumin

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level was 2 g/dL. Twelve patients (55%) had one (n=3) or multiple (n=9) electrolyte abnormalities. Zinc deficiency was documented in 7 patients.

Small bowel bacterial overgrowth was confirmed by culture of duodenal aspirate (>10^5 colony-forming units per milliliter) in 12 patients at some point during clinical evolution. A trial of oral antibiotics was used in 10 patients without clinical benefit (rifaximin in 5, tetracycline in 3, ciprofloxacin in 1, and ciprofloxacin-metronidazole in 1). An additional 2 patients received no therapy for small bowel bacterial overgrowth.

Histologic Findings

In all patients, baseline intestinal biopsies demonstrated villous atrophy with variable degrees of mucosal inflammation (Table 2). Total villous atrophy was observed in 15 patients and partial villous atrophy in 7 patients. A thick band of subepithelial collagen deposition (collagenous sprue) was seen in 7 patients (2 cases had been reported previously[3]). Active/acute inflammation was observed in 15 patients, and increased intraepithelial lymphocytes were found in 14 patients. Aberrant (or clonal) intraepithelial lymphocytes were not detected among the 12 patients tested.

Colonoscopy with random colonic biopsies was performed in 13 patients (59%). Microscopic colitis was found in 5 patients (2 had lymphocytic colitis and 3 had collagenous colitis).

Biopsies of the stomach were available in 14 patients (64%). Lymphocytic gastritis was diagnosed in 5 patients and collagenous gastritis in 2 patients. Chronic gastritis was diagnosed in an additional 7 patients (1 had *Helicobacter pylori* infection).

Treatment and Subsequent Course

Most of the patients in our study had undergone several therapeutic trials, without apparent clinical benefit, before referral to Mayo Clinic, including the use of a gluten-free diet for months (n=20), systemic corticosteroids and/or budesonide (n=20), opioid-derived antidiarrheal agents (most often loperamide) (n=10), pancreatic enzymes (n=4), bile acid sequestrant (n=4), metronidazole (n=4), azathioprine (n=3), and octreotide (n=3).

Clinical response was observed in all 22 patients after suspension of olmesartan. Besides tapering of corticosteroids, no medication was needed to control diarrhea after clinical response was achieved with suspension of the drug. Patients following a gluten-free diet were advised to abandon the diet immediately if they lacked the celiac susceptibility genotypes or to gradually reintroduce gluten if they were HLA-DQ2 or DQ8 positive. No patient had recurrence of symptoms after restarting a gluten-containing diet. Follow-up body weight after suspension of olmesartan was available in 17 patients; 16 had weight gain, with a mean weight gain of 12.2 kg (range, 2.9-28 kg), and 1 patient (patient 5) who had edema at diagnosis lost 4.1 kg during follow-up despite clinical remission.

At the time of this report, follow-up intestinal biopsies have been performed in 18 patients (82%) after a mean of 242.3 days (range, 54-707 days) from the date of suspension of olmesartan. Histologic recovery of the duodenum was documented in 17 patients (Figure). Focal partial villous atrophy was observed in 1 case (patient 2) on a follow-up duodenal biopsy obtained 54 days after suspension of olmesartan. Follow-up gastric biopsies were performed at the same time as repeated biopsy of the duodenum in 6 of the 7 patients with either lymphocytic or collagenous gastritis (no gastric biopsy results were available for patient 11). Follow-up gastric biopsies showed normal mucosa in 4 patients and nonspecific mild chronic gastritis in 2 patients (patients 20 and 22). Follow-up colonoscopies with biopsies of the colon were not performed in the 5 patients with microscopic colitis.

DISCUSSION

We describe a group of patients with unexplained severe spruelike enteropathy while taking olmesartan. We also provide evidence of both clinical and histologic improvement after suspension of olmesartan. Celiac disease was excluded by conventional methods of serology and the absence of clinical response to a gluten-free diet.[17] Other less common enteropathies were excluded (Table 3).

We acknowledge that this case series lacks all the information necessary to prove causality but rather reflects an association. No deliberate rechallenge test with olmesartan was undertaken because of the life-threatening nature of the syndrome, although 2 patients reported anecdotally that their symptoms had worsened when they restarted olmesartan before the potential association was recognized, and 2 patients experienced improvement when olmesartan was stopped when they were hospitalized (for dehydration and hypotension) and worsened in the weeks following discharge and reintroduction of olmesartan. Resolution of the presenting symptoms and subsequent histologic improvement after suspension of olmesartan, in the absence of clinical evidence of other diseases associated with enteropathy, suggest that the association is not likely to be due to chance.

Pathologic findings in the duodenal biopsy can mimic celiac disease or collagenous sprue. Clinicopathologic correlation is advised to confirm the diagnosis of olmesartan-associated enteropathy. Pathologic evidence of involvement of other organs (eg, the

TABLE 2. Histologic Findings in 22 Patients With Spruelike Enteropathy Associated With Olmesartan[a]

Patient No.	Baseline duodenal biopsy results: Villous atrophy	IELs (/100 epithelial cells)[b]	Acute/active inflammation	Thickened collagen band	Aberrant cells/clone[c]	Outcome follow-up duodenal biopsy results	Time d[d]	Other GI findings[e]: Gastric	Colorectal
1	Total	Normal	Yes	No	No/No	Normal	404	Lymphocytic gastritis (HP negative, immunostain)	Collagenous colitis
2	Total	80-100	Yes	Yes	No/NA	Improvement, focal partial villous atrophy	54	Chronic gastritis (HP negative, immunostain)	Normal
3	Total	Normal	Yes	No	No/No	Normal	231	NA	Collagenous colitis
4	Total	40	Yes	Yes	No/No	Normal	263	Collagenous gastritis	NA
5	Total	>100	Yes	No	NA/NA	Normal	54	NA	Normal
6	Partial	60	Yes	No	NA/NA	NA	NA	NA	NA
7	Partial	>100	No	No	No/No	Normal	159	NA	Normal
8	Total	40-60	Yes	No	NA/NA	Normal	143	Lymphocytic gastritis (HP negative, immunostain)	Normal
9	Total	60-80	Yes	No	No/No	Normal	188	NA	NA
10	Partial	Normal	No	No	No/No	Normal	404	NA	NA
11	Partial	50	Yes	No	No/No	NA	NA	Mild lymphocytic gastritis (HP negative, immunostain)	NA
12	Partial	Normal	Yes	No	No/No	Normal, focal active duodenitis	116	Mild active chronic gastritis (HP negative, immunostain)	Mild active chronic colitis
13	Total	40	Yes	Yes	NA/NA	Normal	171	Active chronic gastritis (HP negative, immunostain)	NA
14	Partial	60-80	No	No	NA/NA	Normal	240	Mild active chronic gastritis (HP negative, immunostain)	NA
15	Total	Normal	No	Yes	NA/NA	Normal	181	Mild chronic gastritis (HP negative, no immunostain)	Normal
16	Total	Normal	No	Yes	No/No	Normal	607	Collagenous gastritis	Collagenous colitis
17	Total	40-60	Yes	Yes	No/No	NA	NA	Mild chronic gastritis (HP negative, no immunostain)	Focal acute colitis
18	Partial	Normal	No (marked eosinophilia)	No	NA/NA	NA	NA	NA	NA
19	Total	30	Yes	No	NA/NA	Normal	76	Severe active chronic gastritis and ulceration (HP negative, immunostain)	NA
20	Total	Normal	No	Yes	No/No	Normal	707	Lymphocytic gastritis (HP positive)	Lymphocytic colitis
21	Total	80-100	Yes	No	NA/NA	Normal	179	NA	Lymphocytic colitis
22	Total	80	Yes	No	NA/NA	Normal	184	Lymphocytic gastritis (HP negative, immunostain)	Normal

[a] HP = *Helicobacter pylori*; IELs = intraepithelial lymphocytes; NA = not available.
[b] Normal, <25/100 epithelial cells.
[c] Aberrant cells defined by >50% $CD3^+/CD8^-$ IELs on immunostaining; clone defined by T-cell receptor gene clonal rearrangement by polymerase chain reaction.
[d] Time from suspension of olmesartan to follow-up biopsy.
[e] Any time before suspension of olmesartan.

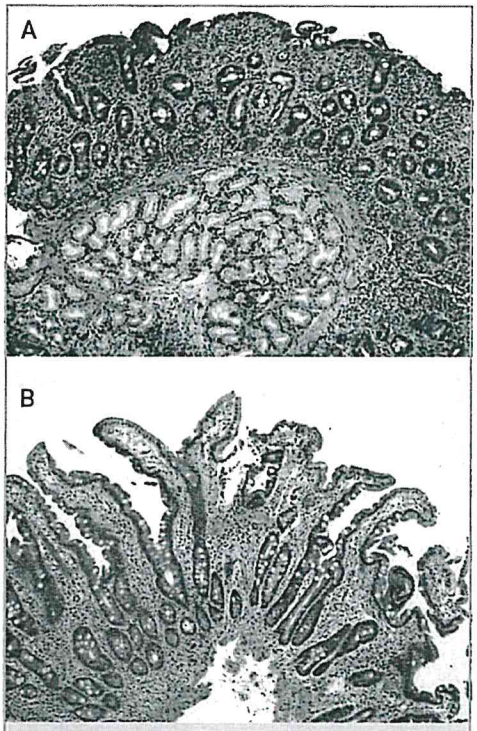

FIGURE. Photomicrographs showing reversible spruelike enteropathy associated with olmesartan (hematoxylin-eosin, original magnification ×100). A, Duodenal biopsy specimen obtained while the patient was taking olmesartan shows total villous atrophy and intraepithelial lymphocytosis. B, Biopsy specimen obtained 6 months after withdrawal of olmesartan and initiation of a gluten-containing diet shows recovery of villi on duodenal mucosa.

stomach and colon) suggests that this disorder may affect the entire gastrointestinal tract. We provide evidence of resolution of inflammation and/or fibrosis in the stomach and duodenum after suspension of olmesartan, implying that these changes are associated with the use of olmesartan. Even though follow-up colonoscopies were not performed in the 5 patients with documented microscopic colitis, clinical remission was achieved in all of these patients, a very unlikely outcome in the presence of persistent inflammation or fibrosis of the colon. Recovery of duodenal mucosa in a relatively short time (median of 8 months from suspension of olmesartan to follow-up biopsies) is a relevant clinical observation because mucosal recovery in other small bowel disorders, such as celiac disease, may take years to occur despite adherence to a gluten-free diet, especially in older adults.[18,19]

Finding small bowel bacterial overgrowth in 12 patients is intriguing and consistent with prior observations of association of small bowel bacterial overgrowth and enteropathy in symptomatic patients with celiac disease.[20,21] The reason for this association is unknown. Thus, although small bowel bacterial overgrowth is a well-recognized cause of chronic diarrhea in the right clinical setting,[22] in this series, the lack of clinical response to oral antibiotics suggests that gastrointestinal symptoms are not explained by the effects of an increased number of bacteria in the small bowel.

The mechanisms underlying olmesartan-associated enteropathy are unknown. The long delay between onset of olmesartan therapy and the development of diarrhea (and enteropathy) suggests cell-mediated immunity damage rather than type I hypersensitivity. Recently, angiotensin receptor blockers have been suggested to have inhibitory effects on transforming growth factor β action.[23,24] Transforming growth factor β is crucially important in the maintenance of gut immune homeostasis.[25,26] Olmesartan is an orally administrated prodrug (olmesartan medoxomil) that is rapidly metabolized to the active component (olmesartan) by esterases in the gastrointestinal mucosa, portal blood, and liver.[27] Nevertheless, the possible role of transforming growth factor β inhibition in olmesartan-associated enteropathy is a question that requires investigation. We do not know if other angiotensin II receptor blockers can be associated with a similar form of enteropathy, but active investigation for similar cases among patients using other drugs of the same class is under way. All our patients with olmesartan-associated enteropathy received antihypertensive drugs from a different class after suspension of olmesartan. HLA-DQ2 was present in 68% of patients with olmesartan-associated enteropathy, a prevalence higher than the 25% to 30% expected for the general population,[28,29] suggesting that perhaps

TABLE 3. Clinical Features of Spruelike Enteropathy Associated With Olmesartan

Gastrointestinal symptoms (eg, chronic diarrhea, weight loss, steatorrhea)
Negative IgA tissue transglutaminase antibodies (or endomysial antibodies)
Evidence of enteropathy (villous atrophy) with or without collagen deposition or intraepithelial lymphocytosis
Lack of clinical response to gluten exclusion
Exclusion of other causes of enteropathy (eg, celiac disease)
Evidence of clinical and histologic improvement after suspension of olmesartan

the presence of HLA-DQ2 may increase the risk of immune-mediated damage in these patients. This may be another example of drug-associated enteropathy of which the medical community should be aware and could result in the identification of several more cases.

CONCLUSION

We report a unique case series to support a novel association between severe spruelike enteropathy and olmesartan. Physicians who encounter patients with diarrheal syndromes should consider medications as a cause, although the potential role for olmesartan had not been considered in these patients by any of the physicians prescribing the medications or treating the diarrheal illness.

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